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Signed P. Mahoney

Dated 28 October 2003

Patents Form 1/77

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040CT02 E752985-2 002934
P01/7700 0.00-0222912.8

1/77

Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
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1. Your reference — 100835

2. Patent application number *(The Patent Office will fill in this part)* — 0222912.8 — 03 OCT 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)*

07957251001

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

NOVEL PROCESS AND INTERMEDIATES

5. Name of your agent *(if you have one)*

Anne Williams

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

08474054001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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Continuation sheets of this form	
Description	19
Claim(s)	06
Abstract	01
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 2/10/2002

Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

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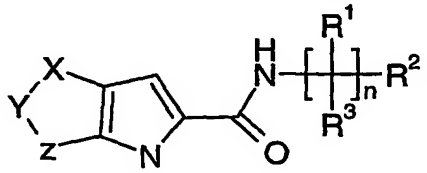
NOVEL PROCESS AND INTERMEDIATES

The present invention relates to a novel process for preparing intermediates for therapeutically effective compounds, together with novel intermediates for use in the process.

Compounds with glycogen phosphorylase activity are described in WO 02/20530. These compounds have a general formula which may be represented as formula (A)

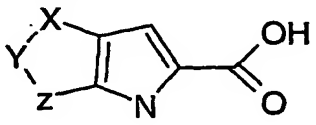


(A)

where X, Y and Z is selected from *inter alia* $-CR^4=CR^5-S-$, R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*,-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino;

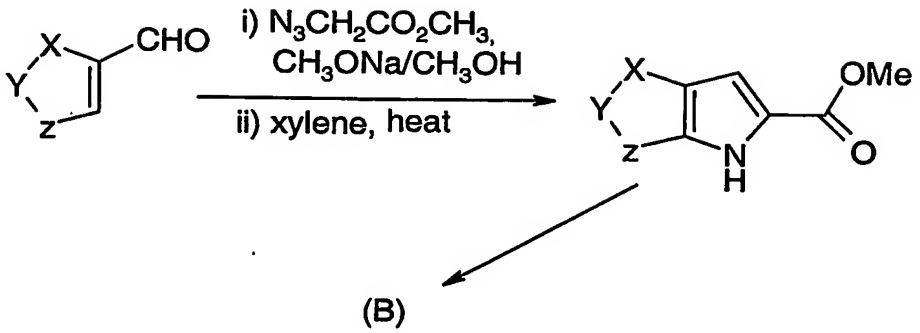
n is 0-4, and R^1, R^2 and R3 are various specified organic groups.

These compounds are generally prepared by a reacting an acid of formula (B)



(B)

with an appropriate amine. Acids of formula (B) are prepared according to the following scheme:

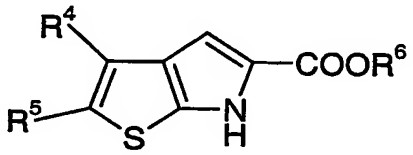


(B)

However, this process is difficult to effect as it may proceed explosively.

The applicants have found an improved process for the production of certain intermediates.

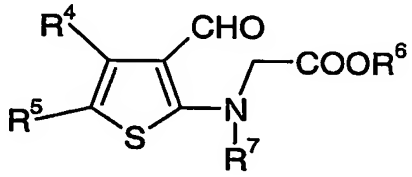
The present invention provides a process for preparing a compound of formula (I)



(I)

where R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, N-(C_{1-6}alkyl)sulphamoyl, N,N,-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-N-(C_{1-6}alkyl)amino; and R^6 is hydrogen or a protecting group,

which process comprises cyclisation of a compound of formula (II)



(II)

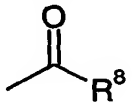
where R^4, R^5 and R^6 are as defined in relation to formula (I) and R^7 is a nitrogen protecting group, and removing protecting group R^7, and thereafter if desired or necessary, removing any protecting group R^6 to obtain the corresponding carboxylic acid.

Cyclisation is suitably effected in an organic solvent such as methanol or dimethylformamide (DMF) in the presence of a base. Suitable bases include particularly strong bases such as an alkali metal alkoxide, for instance sodium methoxide, but also weaker bases such as alkali metal carbonates like potassium carbonate. The reaction is suitably carried out at a broad range of temperatures, for example of from ambient temperature to 70°C, and conveniently at the reflux temperature of the solvent. Under these conditions, R^7 is generally removed in the same reaction step. Depending upon the nature of the group employed however, it might be necessary to remove R^7 in a subsequent step, for example by acid or base hydrolysis reactions.

Acid hydrolysis reactions may be carried out using conventional methods, and in particular using acids such as trifluoromethanesulphonic acid, acetic acid or hydrochloric acid. Base hydrolysis reactions are suitably effected in the presence of bases, such as alkali metal hydroxides, and in particular sodium or potassium hydroxide.

Suitable example of protecting groups R^7 are listed in T.W. Green, Protecting Groups in Organic Synthesis, J. Wiley and Sons, 1991 and in particular are those designated as nitrogen protection groups.

Particular examples of protecting groups R^7 are groups of sub-formula (i)



(i)

where R^8 is a hydrocarbyl or heterocyclic group, either of which may be optionally substituted.

As used herein, the expression "hydrocarbyl" includes any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl such as phenyl or napthyl, arylalkyl such as benzyl, or cycloalkyl, cycloalkenyl or cycloalkynyl. Suitably hydrocarbyl groups contain up to 20 and preferably up to 10 carbon atoms.

The term "aryl" refers to aromatic rings such as phenyl or naphthyl.

The term "heterocyclic" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which, and suitably

from 1 to 4 of which is a heteroatom such as oxygen, sulphur or nitrogen. They may be monocyclic or have fused rings, such a bicyclic or tricyclic ring systems. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, piperidinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

The term "heteroaryl" refers to heterocyclic groups which are aromatic in nature. Thus these may comprises cyclic aromatic hydrocarbons in which one or more carbon atoms have been replaced with a heteroatom. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heteroaryl groups include pyridyl, pyrimidinyl, imidazolyl, thienyl, furyl, pyrazinyl, pyrrolyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, indolyl, isoindolyl, indolizinyl, triazolyl, pyridazinyl, indazolyl, purinyl, quniolizinyl, isoquinolyl, quinolyl phthalazinyl, naphthyridinyl, quinoxalinyl, isothiazolyl and benzo[b]thienyl. Preferred heteroaryl groups are five or six membered rings and contain from one to three heteroatoms.

Suitable optional substituents for heterocyclic and hydrocarbyl groups R^8 include nitro, cyano, halo, oxo, $=CR^{13}R^{14}$, $C(O)_xR^{12}$, OR^{12}, $S(O)_yR^{12}$, $NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $OC(O)NR^{13}R^{14}$, $=NOR^{12}$, $-NR^{12}C(O)_xR^{13}$, $-NR^{12}CONR^{13}R^{14}$, $-N=CR^{13}R^{14}$, $S(O)_yNR^{13}R^{14}$ or $-NR^{12}S(O)_yR^{13}$ where R^{12}, R^{13} and R^{14} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{13} and R^{14} together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_y$ oxygen and nitrogen, x is an integer of 1 or 2, y is 0 or an integer of 1-3. Hydrocarbyl groups R^8 may also include heterocyclic substituents, which may themselves be optionally substituted by one or more of the optional substituents listed above. Heterocyclic groups may also be substituted with hydrocarbyl groups which may also be optionally substituted by any of the groups listed above.

Preferably R^8 is a hydrocarbyl group such as alkyl, aryl or arylalkyl. Most preferably R^8 is a straight chain alkyl group of from 1 to 6 carbon atoms, and particularly is a straight chain C_{1-4}alkyl group, such as methyl.

Particular examples of groups R^4 and R^5 are hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl and C_{1-6}alkanoyloxy.

Suitably R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and C_{1-4}alkanoyloxy.

Preferably R^4 and R^5 are independently selected from hydrogen and halogen such as chlorine, fluorine and bromine, and in particular chlorine.

Most preferably R^4 is hydrogen and R^5 is halogen such as chlorine.

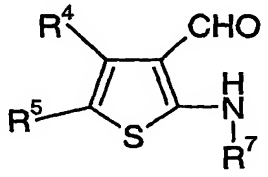
Particular examples of ester protecting groups R^6 are any organic groups which can be removed by hydrogenation or hydrolysis. These include optionally substituted hydrocarbyl or optionally substituted heterocyclic groups. Such groups may be similar to those listed above in relation to R^7.

Suitable example of protecting groups R^6 are also listed in T.W. Green, Protecting Groups in Organic Synthesis, J. Wiley and Sons, 1991 and in particular are those designated as acid protecting groups.

In particular R^6 is a hydrocarbyl group such as C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl such as phenyl, or arylalkyl such as benzyl.

Conversion of a protecting group R^6 to hydrogen is suitably effected using conventional methods, for example as described in WO 02/20530. In particular, the compound is reacted with a base such as lithium hydroxide, in an organic solvent such as methanol, at temperatures of from 20-80°C, and conveniently at the reflux temperature of the solvent.

Compounds of formula (II) are suitably prepared by reacting a compound of formula (III)



(III)

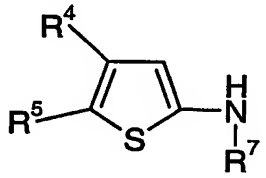
where R^4, R^5 are as defined in relation to formula (I), and R^6 and R^7 are as defined in relation to formula (II), with a compound of formula (IV)

LCH_2COOR^6

(IV)

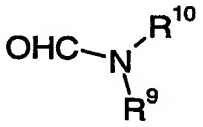
where L is a leaving group such as halogen and in particular bromine. The reaction is suitably effected in the presence of a base in an organic solvent such as dimethylformamide or acetone. Suitable bases include alkali metal carbonates, bicarbonates, hydroxides, or methoxides, but are preferably weak bases such as alkali metal carbonates or bicarbonates, for instance potassium bicarbonate. The reaction may be conducted at elevated temperatures, for example of from 40 to 100°C, preferably from 50 to 70°C and most preferably at about 60°C.

Compounds of formula (III) are suitably prepared by formylation of a compound of formula (V)



(V)

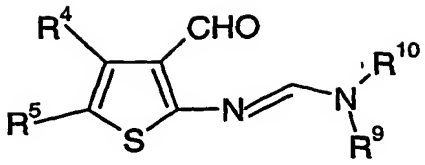
where R^4 and R^5 are as defined above in relation to formula (I) and R^7 is as defined above in relation to formula (II). This can be carried out using conventional methods such as the Vilsmeier-Haack reaction. In this reaction, the compound of formula (V) is reacted with a formyl containing reagent such as a compound of formula (VI)



(VI)

where R^9 and R^{10} are independently selected from phenyl and alkyl groups (in particular lower alkyl groups of 1 to 4 carbon atoms, such as methyl) in the presence of phosphorus oxychloride. The reaction is suitably effected at moderate temperatures and conveniently at room temperature. The compound of formula (VI) may act as a solvent also, where it is for example, DMF, but where this is not possible, a different organic solvent may be used.

The applicants have found however that this reaction produces a significant proportion of an amidine of formula (VII)



(VII)

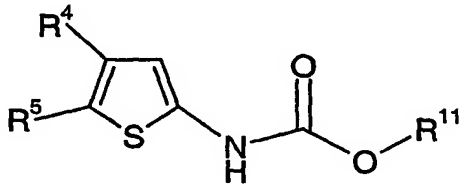
where R^4 and R^5 are as defined in relation to formula (I) and R^9 and R^{10} are as defined in relation to formula (VI). A compound of formula (VII) may be converted to a compound of formula (III) by reaction with a compound of formula (VIII)

$(R^7)_2O$

(VIII)

where R^7 are as defined in relation to formula (II), under acidic conditions, for example in a solvent comprising an organic acid, such as acetic acid. Elevated temperatures for example of from 80-150°C and preferably from 110-130°C are employed. Conveniently the reaction may be effected at the reflux temperature of the solvent. Particular examples of compounds of formula (VIII) are those where groups R^7 are groups of sub-formula (i) as defined above, and in particular where R^8 is methyl, so that the compound of formula (VIII) is acetic anhydride.

Compounds of formula (V) are suitably prepared by reacting a compound of formula (IX)

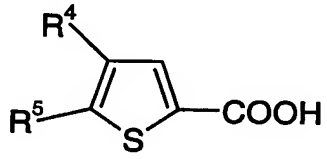


(IX)

where R^4 and R^5 are as defined above in relation to formula (I), and $R^{11}O(C=O)$ is a labile nitrogen protecting group, with a compound of formula (VIII) as defined above, under acidic conditions, for example in a solvent comprising an organic acid, such as acetic acid. Elevated temperatures for example of from 80-150°C and preferably from 110-130°C are employed. Conveniently the reaction may be effected at the reflux temperature of the solvent.

Suitable labile nitrogen protecting groups for $R^{11}O(C=O)$ include tertiary-butoxy carbonyl groups, or benzyloxycarbonyl groups.

Compounds of formula (IX) are either known (see for example Binder et al., Synthesis, (1977, (4) 255-6) or can be prepared from known compounds. In particular, compounds of formula (IX) are suitably prepared by subjecting a compound of formula (X)



(X)

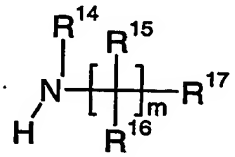
where R^4 and R^5 are as defined in relation to formula (I), to a Curtius rearrangement reaction, in the presence of an alcohol of formula $R^{11}OH$. In this reaction, the compound of formula (X) is reacted with an diphenylphosphorylazide, to convert the acid group to a carbonyl azide, which is thermally decomposed to the amide via an isocyanate. Suitable reaction conditions are illustrated hereinafter.

Compounds of formula (II), (III) and (VII) are novel and form further aspects of the invention.

Compounds of formula (IV), (V), (VI), (VIII), (IX) and (X) are known compounds or they can be prepared from known compounds by conventional methods.

Compounds of formula (I) are suitably used in the production of pharmaceutical compounds and in particular, compounds with glycogen phosphorylase activity as described in WO 02/20530 and EP-A-1088824.

Thus in a further aspect, the invention provides a method as described above, for the production of a compound of formula (I) where R^6 is hydrogen, and further comprising reacting the compound of formula (I) obtained with an amine of formula (XI),



(XI)

where R^{14} is selected from hydrogen or C_{1-8}alkyl,

m is an integer of from 0 to 4,

each R^{15} is the same or different and is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

each R^{16} is the same or different and is selected from is hydrogen or C_{1-6}alkyl;

R^{17} is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO_2-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^aC(O)-, -C(O)NR^a-, -SO_2NR^a-, -NR^aSO_2-, -NR^aC(O)NR^b-, -OC(O)NR^a-, -NR^aC(O)O-, -$NR^aSO_2NR^b$-, -SO_2NR^aC(O)- and -C(O)NR^aSO_2-; wherein R^a and R^b are independently selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V ;

F is C_{1-6}alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C_{3-8}cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said

heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

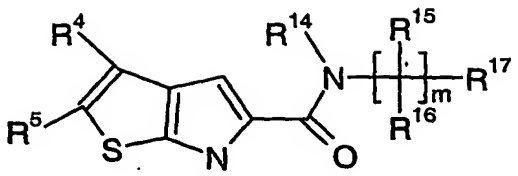
n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

to produce a compound of formula (XII)



(XII)

where R^4, R^5, R^{15}, R^{16}, R^{17} and m are as defined above, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Particular examples of compounds of formula (XII) are compounds where R^{14} is hydrogen, as described in WO 02/20530. For instance, suitable compounds of formula (XII) are compounds where R^4 and R^5 are as defined above, R^{14} is hydrogen, m is 0 and R^{17} is a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is a C_{3-12}cycloalkyl which is optionally fused to a benz ring wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic groups; wherein S may be optionally substituted on carbon by one or more groups selected from V;

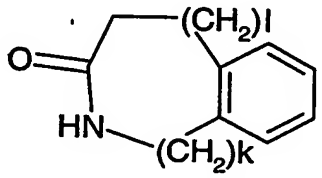
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino , morpholinocarbonyl , *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt thereof.

Other suitable compounds of formula (XII) are compounds where R^4 and R^5 are as defined above, R^{14} is hydrogen, m is 0, and R^{17} is a group -E-F-G-H;

wherein E, F and G are each a direct bond; and

H is a cyclic amide of formula



in which the point of attachment is the carbon atom adjacent to the carbonyl group, k is 0, 1 or 2 and l is 0, 1 or 2 such that the sum of k and l is1, 2 or 3 and wherein one of the carbon atoms governed by k or l may be replaced by sulphur and wherein H is optionally substituted on the carbon atom adjacent to the aromatic ring by a group selected from S and may be independently optionally substituted on nitrogen by a group selected from T;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

T and U are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl,

ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Yet further examples of compounds of formula (XII) are compounds where R^{14} is hydrogen, and wherein R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl,

m is 1; R^{15} is hydrogen or arylC_{1-6}alkyl, R^{16} is hydrogen or C_{1-6}alkyl, and R^{17} is selected from a group -E-F-G-H; wherein E, F and G are each a direct bond;

H is an unsaturated five membered heterocyclic group containing at least one nitrogen atom and one or two ring atoms selected from oxygen and sulphur and wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl and aryl groups;

or a pharmaceutically acceptable salt thereof.

Other particular examples include compounds of formula (XII) where R^{14} is hydrogen, R^4 and R^5 are independently selected from hydrogen, halo or C_{1-6}alkyl.

m is 0; and R^{17} is a group -E-F-G-H;

wherein E is a direct bond;

F is methylene;

wherein G is -C(O)NR^a-, wherein R^a is selected from hydrogen or C_{1-6}alkyl which is optionally substituted by a group V;

H is aryl which may be optionally substituted on carbon by one or more groups selected from S;

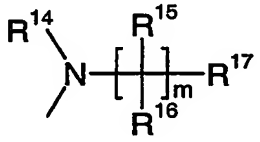
S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl,

C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V ;

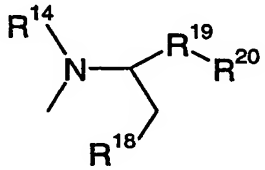
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

or a pharmaceutically acceptable salt thereof.

Other particular compounds of formula (XII) are compounds where the group

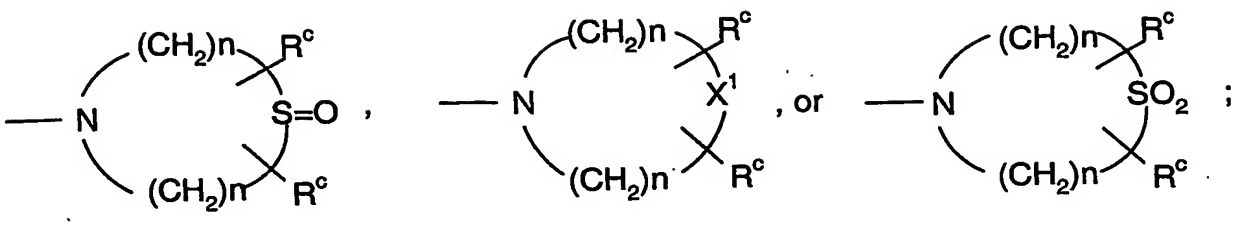


is a group of sub-formula (ii)



(ii)

where R^{14} is as defined above, R^{18} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, R^{19} is a bond or a group –CH(OH)-, and R^{20} is a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is NR^dR^d, $-NR^aCH_2CH_2OR^a$, or



each R^a and R^b is independently hydrogen or $-C_1$-C_8alkyl;

each R^d is independently hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^c is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3, and

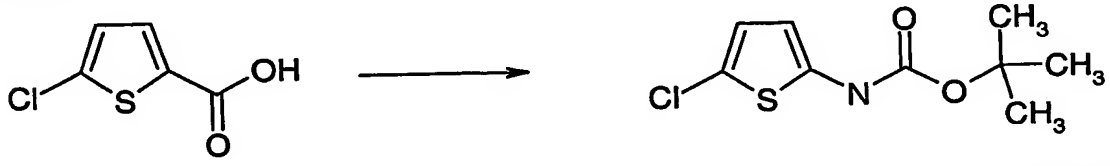
X^1 is NR^a, $-CH_2-$, O or S.

Examples of substituents for aryl and heteroaryl groups Q and R^d include halogen, C_{1-8}alkoxy, C_{1-8}alkyl, trifluoromethyl, amino, mono or di-(C_{1-8}alkyl)amino, nitro, cyano, carboxy or C_{1-8}alkyl esters thereof.

The invention will now be particularly described by way of example.

Example 1

Step 1

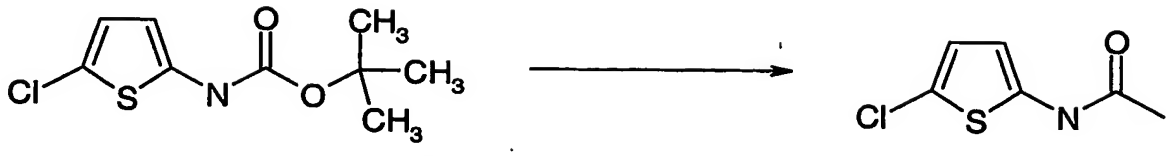


Under argon, 5-chlorothiophene-2-carboxylic acid (5.48g) was dissolved in warm dry tertiary butanol (34ml) and triethylamine (4.7ml) added followed by diphenylphosphorylazide (DPPA) (7.26ml). The mixture was then heated slowly to reflux and refluxed for about 12 hours.

The reaction mixture was then cooled and poured into H_2O (~180ml). The resultant dark suspension was filtered, and the solid was washed with H_2O then dried under suction to a brown powder. This was dissolved in diethyl ether and the solution dried over $MgSO_4$, filtered and evaporated to the desired product, *tert*-butyl (5-chloro-2-thienyl)carbamate, as a dark brown solid (Yield = 6.75g).

^{1}H NMR (400 MHz d^6-DMSO) 6.82 (d, 1H), 6.34 (d, 1H), 1.50 (s, 9H)

Step 2

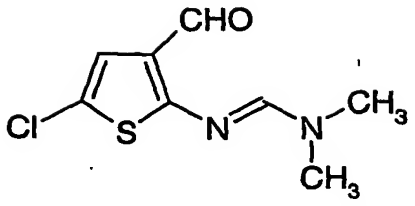


A mixture of acetic anhydride (6.42 ml) in acetic acid (60ml) was added to the product from step 1 (7.48g) and the resultant mixture heated at 120°C for 4 hours. On cooling the reaction mixture was poured into water and extracted with EtOAc. The EtOAc layer was washed with saturated aqueous K_2CO_3, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a black solid. Chromatography through silica using an eluent of CH_2Cl_2 to Et_2O gave *N*-(5-chloro-2-thienyl)acetamide (4.63g, 83%) as a pale brown solid. ^{1}H NMR (400 MHz d^6-DMSO) 11.33 (br s, 1H), 6.82 (d, 1H), 6.40 (d, 1H), 2.05 (s, 3H); ES$^-$ 174.29

Step 3

The product from step 2 (1.09g) was dissolved in DMF (3ml) and cooled in an ice bath. $POCl_3$ (0.58ml) was added dropwise and the dark mixture stirred at 0°C for 30 minutes then allowed to warm to room temperature, and stirred at room temperature for 64 hours.

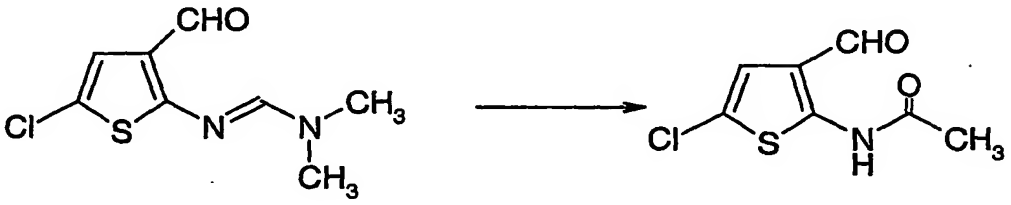
The reaction mixture was poured into ice water and the aqueous phase was extracted into dichloromethane. The dichloromethane layer was dried over $MgSO_4$, filtered and evaporated to a black gum. Purification was effected by suction column chromatography though silica using hexane as initial eluent and CH_2Cl_2 to apply the material to the top of the column. The concentration of diethyl ether was slowly increased (10% jumps) to neat diethyl ether. Several fractions were analysed by LCMS. The 2 fractions which had (MH)+ at 217 and (MH)$^-$ at 202 were combined. They were evaporated to give a yellow solid (0.53g). Spectral analysis both by Lc/ms and ^{1}H nmr showed that this was a mixture of the desired *N*-(5-chloro-3-formyl-2-thienyl)acetamide (87%) and *N'*-(5-chloro-3-formyl-2-thienyl)-*N,N*-dimethylimidoformamide (13%).



^{1}H NMR *N*-(5-chloro-3-formyl-2-thienyl)acetamide (300 MHz d^6-DMSO) 11.65 (br s, 1H), 9.93 (s, 1H), 7.22 (s, 1H), 2.25 (s, 3H); ES$^-$ 202.21;

N'-(5-chloro-3-formyl-2-thienyl)-*N,N*-dimethylimidoformamide (300 MHz d^6-DMSO) 9.90 (s, 1H), 7.97 (s, 1H), 6.93 (s, 1H), 3.13 (s, 3H), 3.02 (s, 3H); ES$^+$ 217.22

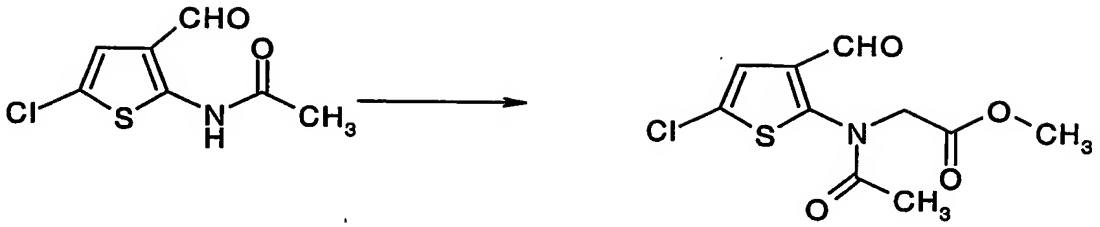
Step 4



The mixture from step 3 (0.53g) was dissolved in acetic acid (5ml) and to this was added acetic anhydride (0.5ml) followed by H_2O (0.25ml). The mixture was heated to reflux for approximately 1 hour whereupon tlc analysis indicated that none of the dimethyl amidine derivative remained.

The reaction mixture was poured into H_2O and the precipitate filtered. The aqueous phase was extracted into a mixture of dichloromethane and methanol in a ratio of 19:1 and the precipitate was dissolved in a similar mixture. The combined organic solutions were washed with dilute aqueous potassium carbonate, ensuring that the pH remained at about 12, then dried over $MgSO_4$. Filtration and evaporation under reduced pressure gave the desired product, *N*-(5-chloro-3-formyl-2-thienyl)acetamide, as a yellow, orange solid (Yield = 0.53g). ^{1}H NMR (300 MHz d^6-DMSO) 11.65 (br s, 1H), 9.93 (s, 1H), 7.22 (s, 1H), 2.25 (s, 3H); ES$^-$ 202.21

Step 5

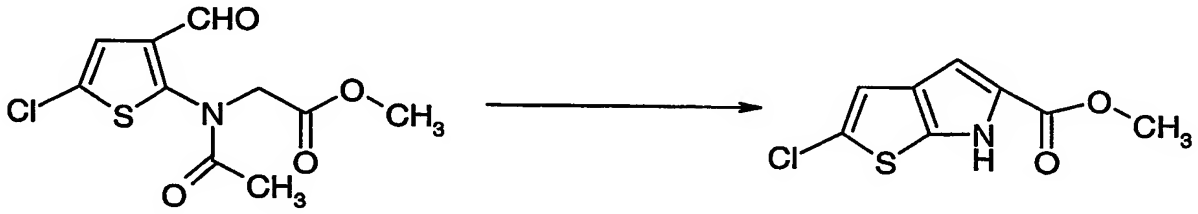


The product from step 4 (460mg) was placed under argon, in dry glassware, and dissolved in dry DMF (2ml). Potassium bicarbonate (567mg) was added to the solution followed by methylbromoacetate (0.54ml). The mixture was heated to 40°C for 150 mins, and then at 60°C for a further 120 mins. The reaction was stirred at room temperature overnight at again heated at 60°C for 270 minutes on the next day.

The product was partitioned between dichloromethane and water and the dichloromethane layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a dark oil. This was purified by suction column chromatography through silica using hexane as initial eluent and CH_2Cl_2 to apply the material to the top of the column. The concentration of CH_2Cl_2 was increased (10% jumps, 50ml fractions) to neat CH_2Cl_2, held at CH_2Cl_2 for a few fractions then the concentration of Et_2O increases (1% jumps) until the spots were removed from the column. The spot corresponding to the desired methyl *N*-acetyl-*N*-(5-chloro-3-formyl-2-thienyl)glycinate (identified using Lc/ms) was collected for use in the subsequent step.

^1H NMR (300 MHz d^6-DMSO) 9.93 (s, 1H), 7.20 (s, 1H), 4.40 (br s, 2H), 3.77 (s, 3H), 2.06 (s, 3H).

Step 6



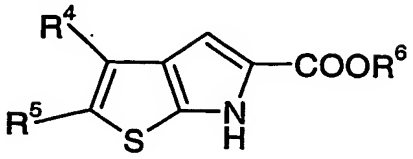
The product from step 5(170mg) was dissolved in MeOH under an argon atmosphere, and a solution of sodium methoxide in methanol (0.62ml of 25% solution) added causing a slight darkening to a brown, clear solution. The mixture was refluxed for about 1 hour.

The reaction mixture was partitioned between dichloromethane and water, and the dichloromethane layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure

to give the desired product, methyl 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate as a yellow solid (Yield = 97mgs (93%). The structure was confirmed by Lc/ms and ^{1}Hnmr spectroscopy. ^{1}H NMR (300 MHz d^6-DMSO) 9.40 (br s, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 3.82 (s, 3H); ES$^-$ 214.16

Claims

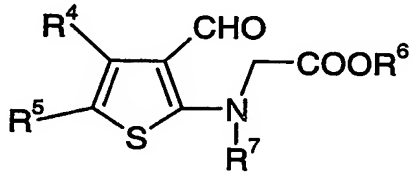
1. A process for preparing a compound of formula (I)



(I)

where R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, N-(C_{1-6}alkyl)sulphamoyl, N, N,-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-N-(C_{1-6}alkyl)amino; and R^6 is hydrogen or a protecting group,

which process comprises cyclisation of a compound of formula (II)

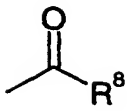


(II)

where R^4, R^5 and R^6 are as defined in relation to formula (I) and R^7 is a nitrogen protecting group, and removing protecting group R^7, and thereafter if desired or necessary, removing any protecting group R^6 to obtain the corresponding carboxylic acid.

2. A process according to claim 1 wherein the protecting group R^7 is removed during the same reaction step as the cyclisation.

3. A process according to claim 1 or claim 2 wherein in structure of formula (II), R^7 is a groups of sub-formula (i)



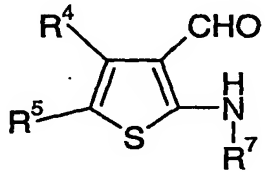
(i)

where R^8 is a straight chain alkyl group of from 1 to 6 carbon atoms.

4. A process according to any one of the preceding claims wherein R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and C_{1-4}alkanoyloxy.

5. A compound of formula (II) as defined in claim 1.

6. A process for preparing a compound according to claim 5 which comprises reacting a compound of formula (III)



(III)

where R^4, R^5 are as defined in claim 1, R^6 and R^7 are as defined in claim 1, with a compound of formula (IV)

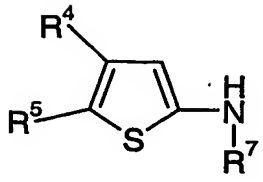
$$LCH_2COOR^6$$

(IV)

where L is a leaving group.

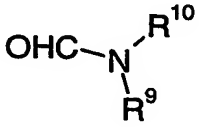
7. A compound of formula (III) as defined in claim 6.

8. A process for preparing a compound according to claim 7 which comprises reacting a compound of formula (V)



(V)

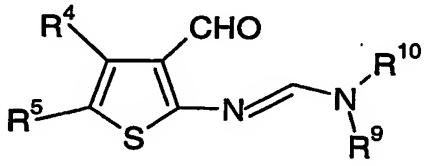
where R^4, R^5 and R^7 are as defined in claim 1, with a compound of formula (VI)



(VI)

where R^9 and R^{10} are alkyl groups in the presence of phosphorus oxychloride.

9. A process for preparing a compound of formula (VII)



(VII)

where R^4 and R^5 are as in claim 1 and R^9 and R^{10} are as defined in claim 8, by reacting a compound of formula (III) as defined in claim 6 with a compound of formula (VIII)

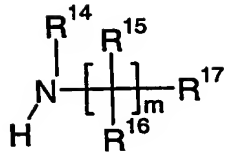
$(R^7)_2O$

(VIII)

where R^7 are as defined in claim 1.

10. A compound of formula (VII) as defined in claim 9.

11. A method according to claim 1 for the production of a compound of formula (I) where R^6 is hydrogen, and further comprising reacting the compound of formula (I) obtained with an amine of formula (XI),



(XI)

where R^{14} is selected from hydrogen or C_{1-8}alkyl,

m is an integer of from 0 to 4,

each R^{15} is the same or different and is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic group and (heterocyclic group)C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

each R^{16} is the same or different and is selected from is hydrogen or C_{1-6}alkyl;

R^{17} is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonylaminocarbonyl, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -SO$_2$-, -OC(O)-, -C(O)O-, -C(O)-, -NR^a-, -NR^{a}C(O)-, -C(O)NR^a-, -SO$_2$NR^a-, -NR^{a}SO$_2$-, -NR^{a}C(O)NR^b-, -OC(O)NR^a-, -NR^{a}C(O)O-, -NR^{a}SO$_2$NR^b-, -SO$_2$NR^{a}C(O)- and

-C(O)NR^{a}SO$_2$-; wherein R^a and R^b are independently selected from hydrogen or C$_{1-6}$alkyl which is optionally substituted by a group V ;

F is C$_{1-6}$alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, C$_{3-8}$cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

n is selected from 0-4; wherein the values of R^1 may be the same or different; and wherein the values of R^3 may be the same or different;

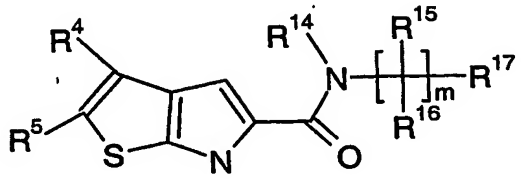
P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{1-6}$alkoxy, C$_{1-6}$alkanoyl, C$_{1-6}$alkanoyloxy, *N*-(C$_{1-6}$alkyl)amino, *N,N*-(C$_{1-6}$alkyl)$_2$amino, C$_{1-6}$alkanoylamino, *N*-(C$_{1-6}$alkyl)carbamoyl, *N,N*-(C$_{1-6}$alkyl)$_2$carbamoyl, *N*-(C$_{1-6}$alkyl)-*N*-(C$_{1-6}$alkoxy)carbamoyl, C$_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, C$_{1-6}$alkoxycarbonyl, C$_{1-6}$alkoxycarbonylamino, *N*-(C$_{1-6}$alkyl)sulphamoyl, *N,N*-(C$_{1-6}$alkyl)$_2$sulphamoyl, C$_{1-6}$alkylsulphonylamino, C$_{1-6}$alkylsulphonyl-*N*-(C$_{1-6}$alkyl)amino, C$_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from C$_{1-4}$alkyl, C$_{1-4}$alkanoyl, C$_{1-4}$alkylsulphonyl, C$_{1-4}$alkoxycarbonyl, carbamoyl, *N*-(C$_{1-4}$alkyl)carbamoyl, *N,N*-(C$_{1-4}$alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl

wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

to produce a compound of formula (XII)



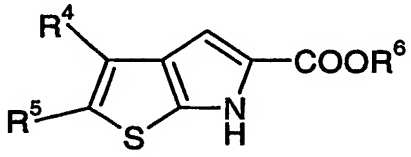
(XII)

where R^4, R^5, R^{15}, R^{16}, R^{17} and m are as defined above, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

A B S T R A C T

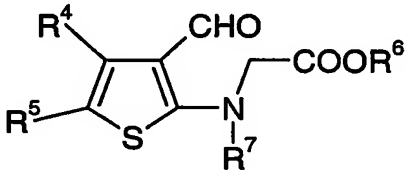
NOVEL PROCESS AND INTERMEDIATES

A process for preparing a compound of formula (I)



(I)

where R^4 and R^5 are as defined in the specification; and R^6 is hydrogen or a protecting group, which process comprises cyclisation of a compound of formula (II)



(II)

where R^4, R^5 and R^6 are as defined in relation to formula (I) and R^7 is a nitrogen protecting group, and removing protecting group R^7, and thereafter if desired or necessary, removing any protecting group R^6 to obtain the corresponding carboxylic acid.

Novel intermediates and the use of the products in the preparation of pharmaceutical compounds is also described and claimed.